Claims 28-30 stand rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 8, 16 and 27 of U.S. Patent No. 6,326,358. Applicant will address this rejection in due course, upon the indication of otherwise allowable subject matter in the present application.

Claims 28-30, 35-38, 40-43, and 45-51 stand rejected under 35 U.S.C. 112, first paragraph, for alleged lack of enablement on the basis that there is no written description of what constitutes "a group that enhances the pharmacodynamic properties of oligonucleotides or a group that enhances the pharmacokinetic properties of oligonucleotides." In as much as these terms do not appear in the presently amended claims, Applicant respectfully requests withdrawal of the rejection.

Claims 28-30 and 34-51 stand rejected under 35 U.S.C. §112, first paragraph, apparently for the reason that the specification allegedly does not provide enablement for methods of treating organisms having a disease characterized by the undesired production of a protein. Applicant traverses the rejection and respectfully requests reconsideration because the invention is sufficiently enabled by the specification.

Applicant would like to thank the Examiner for pointing out that methods for inhibiting the production of a protein (*i.e.,* translation of ICAM-1, which has been associated with a variety of diseases and disorders[1]) *in vitro* according to the present invention are enabled by the specification. The Office Action, however, mistakenly concludes from a few select references (Branch, Agrawal, Gewirtz, *et al.*, Tamm et al.) that the state of antisense-mediated gene inhibition methods *in vivo* for treatment of

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[1] The expression of ICAM-1 has been associated with a variety of skin disorders such as allergic contact dermatitis, fixed drug eruption, lichen planus and psoriasis (Ho *et al.*, *J. Am. Acad. Dermatol.,* 1990, *22*, 64; Griffiths *et al.*, *Am. J. Pathology,* 1989, *135*, 1045; Lisby *et al.*, *Br. J. Dermatol.,* 1989, *120*, 479; Shiohara *et al.*, *Arch. Dermatol.,* 1989, *125*, 1371; Regezi *et al.*, *Oral Surg. Oral Med. Oral Pathol.*, 1996, *81*, 682). Moreover, intraperitoneal administration of a monoclonal antibody to ICAM-1 decreases ovalbumin-induced eosinophil infiltration into skin in mice (Hakugawa *et al.*, *J. Dermatol.*, 1997, *24*, 73). Antisense compounds targeted to ICAM-1 are described in U.S. Patents Nos. 5,514,788 and 5,591,623, and co-pending U.S. patent applications Serial Nos. 09/009,490 and 09/062,416, January 20, 1998 and April 17, 1998, respectively, all to Bennett *et al.* [Specification, paragraph bridging pages 37-38]

diseases is highly unpredictable, especially in regard to oligo uptake by cells, toxicity, and immunological problems. In support of this assertion, the Office Action additionally provides Braasch *et al.*, *Biochemistry*, **2002**, April; 41(14): 4503-4510, allegedly representing the problematic state of the art even after the priority date of the present application. These references mischaracterize the state of the art because they emphasize the failures and difficulties of oligonucleotide therapy without equally addressing the successful advances in the field. In fact, oligonucleotide therapy is demonstrably successful long before the earliest priority date of the present application, and successful delivery and activity of therapeutic oligonucleotides **in organisms** are described repeatedly in the literature. For example, Offensperger *et al.*, *EMBO J.*, **1993**, *12*, 1257-1262, a copy of which is enclosed herewith, disclose a phosphorothioate-modified antisense oligonucleotide directed against duck hepatitis B virus that, when administered intravenously to ducks, resulted in complete inhibition of virus replication and viral gene expression. Simons *et al.*, *Nature*, **1992**, *359*, 67-70, a copy of which is enclosed herewith, report that a phosphorothioate-modified c-myb antisense oligonucleotide is effective as a suppressor of smooth muscle cell proliferation, both *in vitro* in smooth muscle cells in culture and *in vivo* in the carotid artery of rats. Kitajima *et al.*, *Science*, **1992**, *258*, 1792-1795, a copy of which is enclosed herewith, discloses antisense oligonucleotides that exhibit *in vivo* efficacy upon subcutaneous or intraperitoneal injection in mice.

In addition, Applicant encloses herewith copies of 1) Monia *et al.*, *Nature Med.*, **1996**, *2*, 668, 2) Oberbauer *et al.*, *Proc. Natl. Acad. Sci. USA*, **1996**, *93*, 4903, 3) Monia *et al.*, *Proc. Natl. Acad. Sci. USA.*, **1996**, *93*, 15481, 4) Cucco *et al.*, *Cancer Res.*, **1996**, *56*, 4332, 5) Offensperger *et al.*, Antisense Therapy of Hepatitis B Virus Infection, **1996**, Agrawal Ed., Humana Press Inc. Tolowa, NJ, pp. 143-158, 6) Sun *et al.*, *Br. J. Pharmacol.*, **1996**, *118*, 131, 7) Neurath *et al.*, *Nature Med.*, **1996**, *2*, 998-1004, 8) Leonetti *et al.*, *J. N.C.I.*, **1996**, *88*, 419, and 9) Del Bufalo *et al.*, *Br. J. Cancer*, **1996**, *74*, 387, each of which demonstrate successful administration of oligonucleotides via the bloodstream or local administration. Each of these references shows that oligonucleotides administered to the bloodstream reach their target destinations as well as modify

expression of a protein. Thus, successful *in vivo* delivery and activity of oligonucleotides has been overwhelmingly demonstrated for the treatment of diseases.

The Office Action also improperly asserts on page 7, apparently for the reason that Example 3 recites a model *in vitro* exemplification of the present invention, that "the specification as filed fails to provide any guidance which resolves the known unpredictability in the art associated with appropriate *in vivo* delivery and treatment effects provided by... [Applicant's claimed invention]." Applicant respectfully traverses this assertion since there is no such requirement in the Patent Law under 35 U.S.C. § 112, paragraph 1. And even if the Patent Law has such a requirement (and Applicant is not conceding that it does), Applicant also traverses this rejection for the reason that the specification enables ***the skilled artisan*** to carry out Applicant's claimed methods for the treatment and prevention of diseases associated with undesired protein production in *in vivo* environments.

Not only has successful oligonucleotide therapy been well known to those skilled in the art at the time of filing, but Examples 3 and 4 of the present application also provide ample enablement for using antisense oligonucleotides to modulate protein expression *in vivo*. Specifically, Example 3 reports experimental data for ICAM-1 expression in HUVEC cells which serve as ***models*** for *in vivo* systems, and Example 4 reports the *in vivo* results of pharmacokinetic studies of oligonucleotides in rats showing effective delivery and systemic distribution of oligonucleotides. Accordingly, the office action mistakenly asserts that the specification as filed does not provide any guidance or examples that would enable a skilled artisan to treat or prevent any diseases or conditions suspected of being associated with undesired protein production in *in vivo* environments.

In view of the evidence provided above, it is clear that the state of the art was indeed advanced to the point that further experimentation, if necessary, would have been routine to one skilled in the art at the time of filing. Thus, the specification is enabling for the entire scope of the claims, including both *in vitro* and *in vivo* embodiments. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 28-30 and 34-51 under 35 U.S.C. §112, first paragraph.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

Respectfully submitted,

Jeffrey H. Rosedale, Ph.D., Esq.
Registration No. 46,018

Date: September 3, 2002

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Philadelphia, PA 19103
(215) 568-3100

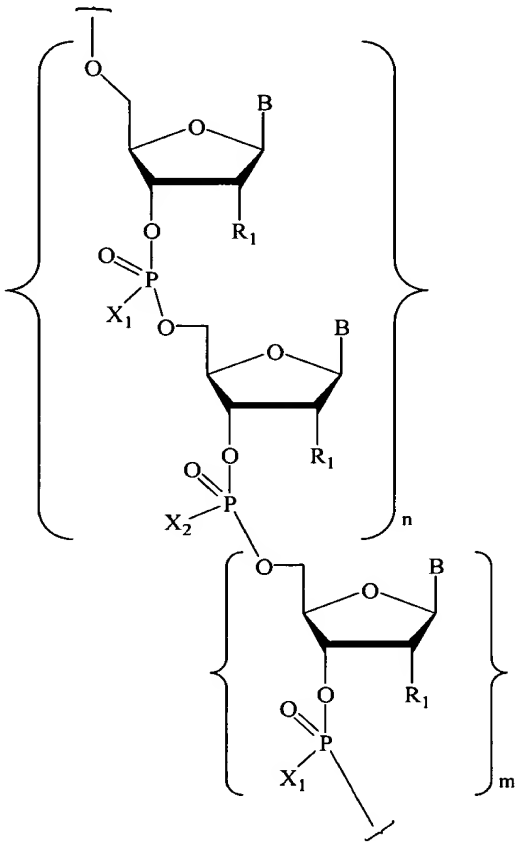
SEP 0 3 2002
PATENT & TRADEMARK OFFICE

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Please amend claims 28-30 as follows:

28. (amended twice) A method of treating an organism having a disease characterized by the undesired production of a protein, said method comprising contacting said organism with a compound of formula:



wherein:

each B is a nucleobase;

one of X_1 or X_2 is O, and the other of X_1 or X_2 is S;

each R_1, is, independently, H, hydroxyl, C_1-C_{20} alkyl, C_3-C_{20} alkenyl, C_2-C_{20} alkynyl, halogen, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, or polyether;

or R_1 is a group of formula $Z\text{-}R_{22}\text{-}(R_{23})_v$;

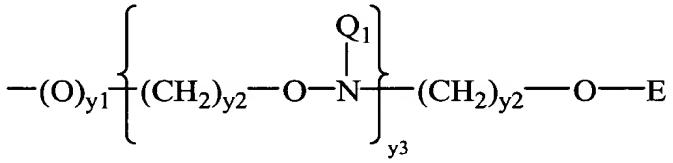
Z is O, S, NH, or $N\text{-}R_{22}\text{-}(R_{23})_v$;

R_{22} is C_1-C_{20} alkyl, C_2-C_{20} alkenyl, or C_2-C_{20} alkynyl;

R_{23} is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, or polyether[, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides];

v is from 0 to about 10;

or R_1 has the formula:



wherein:

y1 is 0 or 1;

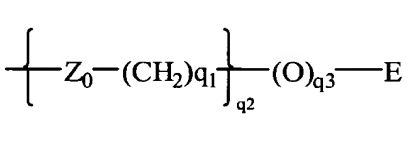
y2 is independently 0 to 10;

y3 is 1 to 10;

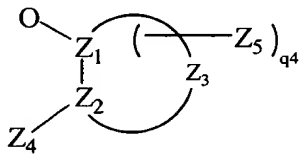
E is C_1-C_{10} alkyl, $N(Q_1)(Q_2)$ or $N{=}C(Q_1)(Q_2)$;

each Q_1 and Q_2 is, independently, H, C_1-C_{10} alkyl, substituted alkyl, dialkylaminoalkyl, a nitrogen protecting group, a tethered or untethered conjugate group, a linker to a solid support; or Q_1 and Q_2, together, are joined in a nitrogen protecting group or a ring structure that can include at least one additional heteroatom selected from N and O;

or R_1 has one of formula I or II:



I



II

wherein:

Z_0 is O, S, or NH;

q^1 is from 0 to 10;

q^2 is from 1 to 10;

q^3 is 0 or 1;

q^4 is, 0, 1 or 2;

Z_4 is OM_1, SM_1, or $N(M_1)_2$;

each M_1 is, independently, H, C_1-C_8 alkyl, C_1-C_8 haloalkyl, $C(=NH)N(H)M_2$, $C(=O)N(H)M_2$ or $OC(=O)N(H)M_2$;

M_2 is H or C_1-C_8 alkyl;

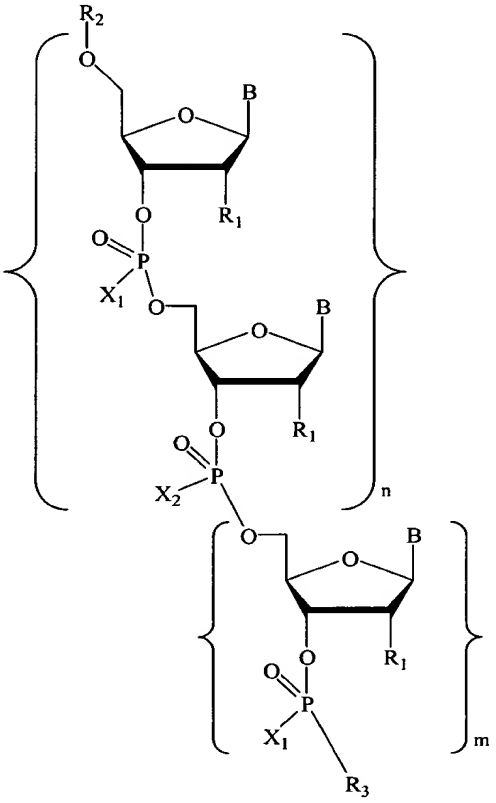
Z_1, Z_2 and Z_3 comprise a ring system having from about 4 to about 7 carbon atoms, or having from about 3 to about 6 carbon atoms and 1 or 2 hetero atoms wherein said hetero atoms are selected from oxygen, nitrogen and sulfur, and wherein said ring system is aliphatic, unsaturated aliphatic, aromatic, or saturated or unsaturated heterocyclic; and

Z_5 is alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14 carbon atoms, $N(Q_1)(Q_2)$, OQ_1, halo, SQ_1 or CN;

n is from 2 to 50; and

m is 0 or 1.

29. (amended twice) A method of treating an organism having a disease characterized by the undesired production of a protein, said method comprising contacting said organism with a compound of formula:



wherein:

each B is a nucleobase;

X_1 is S;

X_2 is O;

each R_1, is, independently, H, hydroxyl, C_1-C_{20} alkyl, C_3-C_{20} alkenyl, C_2-C_{20} alkynyl, halogen, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-

aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, or polyether;

or R_1 is a group of formula $Z\text{-}R_{22}\text{-}(R_{23})_v$;

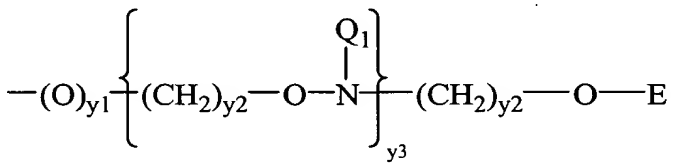
Z is O, S, NH, or $N\text{-}R_{22}\text{-}(R_{23})_v$;

R_{22} is $C_1\text{-}C_{20}$ alkyl, $C_2\text{-}C_{20}$ alkenyl, or $C_2\text{-}C_{20}$ alkynyl;

R_{23} is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, or polyether[, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides];

v is from 0 to about 10;

or R_1 has the formula:



y1 is 0 or 1;

y2 is independently 0 to 10;

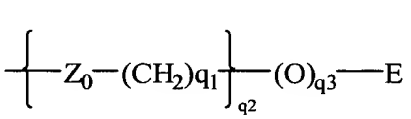
y3 is 1 to 10;

E is $C_1\text{-}C_{10}$ alkyl, $N(Q_1)(Q_2)$ or $N{=}C(Q_1)(Q_2)$;

each Q_1 and Q_2 is, independently, H, $C_1\text{-}C_{10}$ alkyl, substituted alkyl, dialkylaminoalkyl, a nitrogen protecting group, a tethered or untethered conjugate group, a linker to a solid support; or Q_1 and Q_2, together, are joined in a

nitrogen protecting group or a ring structure that can include at least one additional heteroatom selected from N and O;

or R_1 has one of formula I or II:



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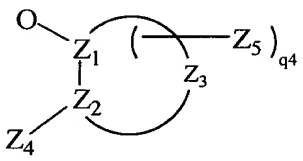


II

wherein:

Z_0 is O, S, or NH;

q^1 is from 0 to 10;

q^2 is from 1 to 10;

q^3 is 0 or 1;

q^4 is, 0, 1 or 2;

Z_4 is OM_1, SM_1, or $N(M_1)_2$;

each M_1 is, independently, H, C_1-C_8 alkyl, C_1-C_8 haloalkyl, $C(=NH)N(H)M_2$, $C(=O)N(H)M_2$ or $OC(=O)N(H)M_2$;

M_2 is H or C_1-C_8 alkyl;

Z_1, Z_2 and Z_3 comprise a ring system having from about 4 to about 7 carbon atoms, or having from about 3 to about 6 carbon atoms and 1 or 2 hetero atoms wherein said hetero atoms are selected from oxygen, nitrogen and sulfur, and wherein said ring system is aliphatic, unsaturated aliphatic, aromatic, or saturated or unsaturated heterocyclic; and

Z_5 is alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14 carbon atoms, $N(Q_1)(Q_2)$, OQ_1, halo, SQ_1 or CN;

n is from 2 to 50; and

m is 0 or 1;

R_2 is H, a hydroxyl protecting group, or an oligonucleotide; and

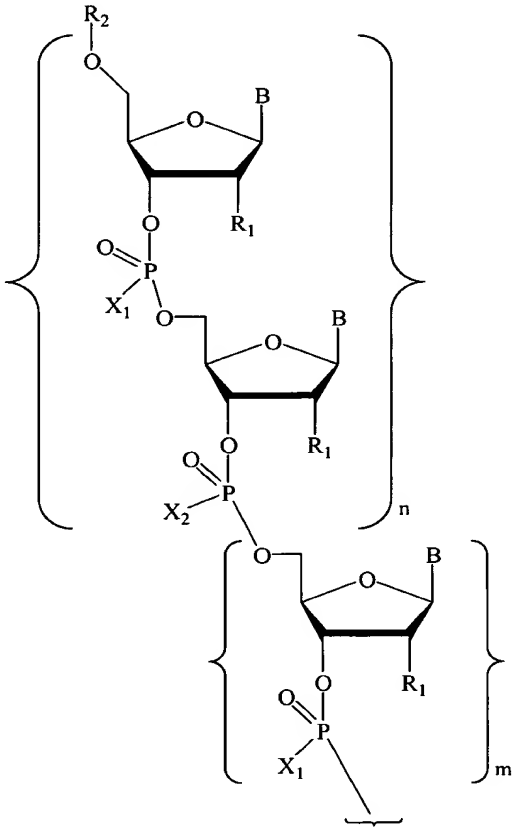
R_3 is OH, an oligonucleotide, or a linker connected to a solid support.

30. (amended twice) A method of treating an organism having a disease characterized by the undesired production of a protein, said method comprising_contacting said organism with a compound of formula:

(5') W^1-W^2-W^3 (3')

wherein:

W^1 has the Formula:



wherein:

each B is a nucleobase;

one of X_1 or X_2 is O, and the other of X_1 or X_2 is S;

each R_1, is, independently, H, hydroxyl, C_1-C_{20} alkyl, C_3-C_{20} alkenyl, C_2-C_{20} alkynyl, halogen, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, or polyether;

or R_1 is a group of formula Z-R_{22}-$(R_{23})_v$;

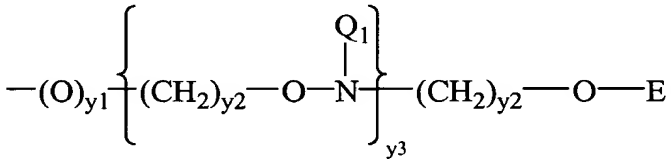
Z is O, S, NH, or N-R_{22}-$(R_{23})_v$;

R_{22} is C_1-C_{20} alkyl, C_2-C_{20} alkenyl, or C_2-C_{20} alkynyl;

R_{23} is hydrogen, amino, halogen, hydroxyl, thiol, keto, carboxyl, nitro, nitroso, nitrile, trifluoromethyl, trifluoromethoxy, O-alkyl, S-alkyl, NH-alkyl, N-dialkyl, O-aryl, S-aryl, NH-aryl, O-aralkyl, S-aralkyl, NH-aralkyl, amino, N-phthalimido, imidazole, azido, hydrazino, hydroxylamino, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocycle, carbocycle, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, or polyether[, a group that enhances the pharmacodynamic properties of oligonucleotides, or a group that enhances the pharmacokinetic properties of oligonucleotides];

v is from 0 to about 10;

or R_1 has the formula:



y1 is 0 or 1;

y2 is independently 0 to 10;

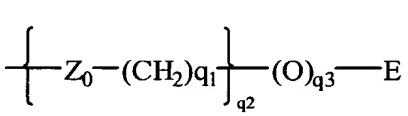
y3 is 1 to 10;

E is C_1-C_{10} alkyl, $N(Q_1)(Q_2)$ or $N{=}C(Q_1)(Q_2)$;

each Q_1 and Q_2 is, independently, H, C_1-C_{10} alkyl, substituted alkyl, dialkylaminoalkyl, a nitrogen protecting group, a tethered or untethered

conjugate group, a linker to a solid support; or Q_1 and Q_2, together, are joined in a nitrogen protecting group or a ring structure that can include at least one additional heteroatom selected from N and O;

or R_1 has one of formula I or II:



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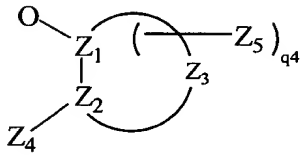


II

wherein:

Z_0 is O, S, or NH;

q^1 is from 0 to 10;

q^2 is from 1 to 10;

q^3 is 0 or 1;

q^4 is, 0, 1 or 2;

Z_4 is OM_1, SM_1, or $N(M_1)_2$;

each M_1 is, independently, H, C_1-C_8 alkyl, C_1-C_8 haloalkyl, $C(=NH)N(H)M_2$, $C(=O)N(H)M_2$ or $OC(=O)N(H)M_2$;

M_2 is H or C_1-C_8 alkyl;

Z_1, Z_2 and Z_3 comprise a ring system having from about 4 to about 7 carbon atoms, or having from about 3 to about 6 carbon atoms and 1 or 2 hetero atoms wherein said hetero atoms are selected from oxygen, nitrogen and sulfur, and wherein said ring system is aliphatic, unsaturated aliphatic, aromatic, or saturated or unsaturated heterocyclic; and

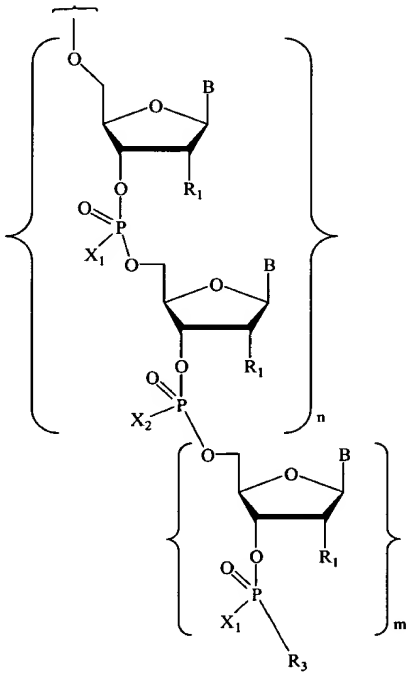
Z_5 is alkyl or haloalkyl having 1 to about 10 carbon atoms, alkenyl having 2 to about 10 carbon atoms, alkynyl having 2 to about 10 carbon atoms, aryl having 6 to about 14 carbon atoms, $N(Q_1)(Q_2)$, OQ_1, halo, SQ_1 or CN;

n is from 2 to 50; and

m is 0 or 1;

R_2 is H, a hydroxyl protecting group, or an oligonucleotide;

W^3 has the Formula:



wherein R_3 is OH, an oligonucleotide, or a linker connected to a solid support; and

W^2 is a plurality of covalently bound nucleosides linked by phosphodiester or phosphorothioate linkages.